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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/325,189	06/03/1999	MASATAKA KINJO	990360/LH	2516

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EXAMINER

TUNG, JOYCE

ART UNIT PAPER NUMBER

1637

DATE MAILED: 07/13/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

34.

**Office Action Summary****Application No.**

09/325,189

**Applicant(s)**

KINJO, MASATAKA

**Examiner**

Joyce Tung

**Art Unit**

1637

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
 Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 30 March 2004.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-4, 7-39, 42 and 43 is/are pending in the application.
- 4a) Of the above claim(s) 9-38 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-4, 7, 8, 39, 42 and 43 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)  | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                                   | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)             |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____  |

### **DETAILED ACTION**

The applicant's response filed 2/2/2004 has been entered. Claims 1-4, 7-39 and 42-43 are pending and claims 9-38 are withdrawn from further consideration.

#### ***Continued Examination Under 37 CFR 1.114***

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/30/2004 has been entered.

#### ***Claim Rejections - 35 USC § 112***

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 1-4, 7-8, 39 and 42-43 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 1-4, 7-8, 39 and 42-43 are vague and indefinite because of the phrase "the other primer". It is unclear whether or not there is a third primer, which is in the reaction. Clarification is required.

#### ***Claim Rejections - 35 USC § 103***

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are

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such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

5. Claims 1-5, 7-8, 39 and 42-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Salituro et al. (6,391,544, issued May 21, 2002) in view of Eigen et al. (5,807,677, issued September 15, 1998) and in view of McCabe (PCR Protocols: A Guide to Methods and Applications, 1990, pg. 76-83).

Salituro et al. disclose a method for detecting a target sequence in a test sample employing a pair of primer sequences to generate copies of the target sequence (See column 1, lines 7-10). The first primer and second primer are referred to as a "primer pair" (See column 3, lines 21-23). The first primer is added to the amplification mixture such that its concentration is between 15% to 250% greater than the concentration of the second primer (See column 3, lines 61-64). If desired, a primer can be labeled using methodologies well known in the art (See column 4, lines 12-13). The label can be detectable label, for example fluorophores (See column 5, lines 35-39). The labeled primer was at a concentration of 50 nM and the unlabeled primer concentration was varied at the concentration 25, 37.5, 50 or 62.5 nM. The experiments results are that when the unlabeled primer is present at concentration lower than the labeled primer, higher signals are achieved at higher target concentration and when the concentration of unlabeled primer is higher than or equal to the concentration of labeled primer, the higher signals are achieved at medium target concentration (See column 8, lines 18-40).

Salituro et al. do not explicitly disclose the nucleic acid amplification reaction being performed until the primer present in a lower number is consumed.

However, McCabe discloses an asymmetric PCR in which during the initial 15-25 cycles, most of the product generated is double stranded and accumulates exponentially and as the low concentration primer becomes depleted, further cycles generate an excess of one of the two strands, depending on which of the amplification primer was limited (See pg. 77-83).

Salituro et al. do not disclose evaluating a fluctuation motion of the amplified nucleic acid to quantifying the target nucleic acid and specific ratio the concentration of the primers as claimed in claims 42-43.

Eigen et al. disclose fluorescence correlation spectroscopy (FCS) method, which requires a specific primer sequence, marked with fluorescence dye (See column 2, lines 31-32). The measuring principle with FCS is based on the fact that fluorogenic molecules can be measured in extremely diluted solutions by exposing a small volume element of the solution (See column 2, lines 38-41). The fluorescence correlation spectroscopy (FCS) has a number of advantages compared to the PCR method in which FCS can be used for both single stranded and double stranded nucleic acid molecules and is more direct identifying the individual nucleic acids (See column 3, lines 46-57).

Since the method of Salituro et al. provides the quantitative signal of the labeled amplified nucleic acid products (See column 8, lines 30-40), one of ordinary skill in the art would have been motivated to apply the FCS method to the method of Salituro et al. at the time of the instant invention. The motivation is based upon the discussion of the advantage of using FCS as addressed by Eigen et al. above. Moreover, although Salituro et al. do not disclose the specific ratio of the concentration of the primers as claimed in claims 42-43, Salituro et al. do disclose the comparison experiment using different ratio concentration of two different primers. Thus, one of ordinary skill in the art would have optimized the concentration ratio of the two primers based upon the teachings of Salituro et al. It would have been prima facies obvious to carry out the method as claimed.

The response filed 2/2/2004 argues that the amplified double stranded nucleic acid is labeled, whereas a single stranded nucleic acid product is not labeled. Based upon the presentation of fig. 3, it is unclear that why the amplified double stranded nucleic acid is labeled,

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whereas a single stranded nucleic acid product is not labeled because as presented in the claims, the primer present in a lower number is labeled and consumed.

The response further argues that Salituro et al. do not disclose the same asymmetric PCR as the presently claimed invention. However, the teachings of Salituro et al. read on the limitations of the claims (See column 8, lines 30-40).

The response also argues that the method of the present invention, only when the amount of labeled primer is lower than that of unlabeled primer, the phenomenon where free-labeled primer is consumed with the progress of a PCR amplification is observed. The claims do not require that the free-labeled primer is consumed with the progress of a PCR amplification.

The response argues that Eigen et al. do not teach or suggest combining FCS with PCR. However, Eigen et al. do disclose that FCS can be used for both single stranded and double stranded nucleic acid molecules detection and is more direct identifying the individual nucleic acids from PCR (See column 3, lines 46-57).

Thus, Applicant's arguments filed 2/2/2004 have been fully considered but they are not persuasive as discussed above.

#### Summary

6. No claims are allowable.

7. Any inquiries concerning this communication or earlier communications from the examiner should be directed to Joyce Tung whose telephone number is (703) 305-7112. The examiner can normally be reached on Monday-Friday from 8:00 AM-4:30 PM.

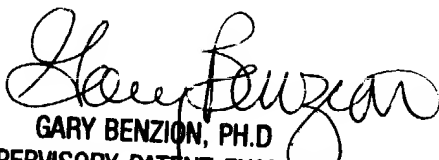
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached at (703) 308-1119 on Monday-Friday from 10:00 AM-6:00 PM.

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Any inquiries of a general nature or relating to the status of this application should be directed to the Chemical/Matrix receptionist whose telephone number is (703) 308-0196.

8. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Art Unit 1637 via the PTO Fax Center located in Crystal Mall 1 using (703) 305-3014 or 308-4242. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989).

Joyce Tung JT  
July 1, 2004

  
GARY BENZION, PH.D  
SUPERVISORY PATENT EXAMINER  
TECHNOLOGY CENTER 1600  
7/12/04